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Editorial overview 'Network news: Reporting from the frontlines of cell signaling'

Andrea Ablasser and Jeremy Thorner

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This review comes from a themed issue on **Cell Signalling**

Edited by **Andrea Ablasser** and **Jeremy W. Thorner**

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Andrea Ablasser is an associate professor of immunology at the Swiss Federal Institute of Technology in Lausanne. Major goals of her research are understanding how the human innate immune system detects pathogens and the mechanisms raised to defend against them, especially immunorecognition of foreign DNA by the cGAS-STING signaling pathway. Her most recent accolade for her contributions to understanding fundamental mechanisms in innate immunity is the prestigious Sanofi-Institut Pasteur International Junior Award (2019).

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Jeremy Thorner is a professor of biochemistry, biophysics, and structural biology in the Department of Molecular and Cell Biology at the University of California, Berkeley. His research conducted over many years with budding yeast has elucidated conserved transmembrane and intracellular signal transduction mechanisms controlling cell growth and division, cell morphology, and gene expression. For his work, he recently received the Herbert Tabor Research Award from the American Society for Biochemistry and Molecular Biology (2019).

Signal transduction processes can be viewed, quite justifiably, as the higher command functions executed by cells. Signaling events regulate metabolism (both catabolic and biosynthetic), the actions of numerous macromolecular complexes, and the biogenesis and operation of organellar compartments. Such information transmission allows an organism to maintain homeostasis and adjust cell number, cell behavior, and organismal physiology appropriately in response to a wide variety of external stimuli. Conversely, metabolites, organelles, and other cellular components serve as or emit internal cues that also control cell function and behavior. Thus, elucidating the interconnected networks of signal transduction mechanisms in different cell types is a primary mission of all of the various disciplines by which we interrogate cells, tissues, and organisms — from biochemistry and structural biology to development, endocrinology, systems biology, pharmacology, neuroscience, immunology, and cancer biology.

Our objective in this 'Cell Signaling' issue of *Current Opinion in Cell Biology* is, therefore, to highlight recent advances in our fundamental understanding of signaling mechanisms and the state-of-the-art methods available to assess these processes, across the breadth and sweep of current research. The articles in this issue, each written by internationally acknowledged experts, either emphasize the principles and applications of tools used to analyze signaling or describe the molecular basis of a signaling process *per se*, its logic, and its physiological consequences in controlling a particular aspect of cell biology.

With regard to tools for interrogating signaling events, **Jonathan Swietlik, Ankit Sinha, and Felix Meissner** (Max Planck Institute, Martinsried, Germany) highlight recent advances in mass spectrometry—based methods that now permit comprehensive interrogation of the entire proteome as a means to assess globally and systematically the changes in protein content and modification state elicited during any physiological transition. **Jin Zhang, Ha Neul Lee, and Sohum Mehta** (Univ. of California, San Diego, La Jolla, USA) discuss basic concepts and recent advances in the development and application of genetically encoded fluorescent biosensors for monitoring the spatiotemporal dynamics of signaling molecules, as well as optogenetic devices for manipulating signaling activity, in live cells in real time.

Another challenge in modern signal transduction research is teasing out the multifarious roles that particular molecules involved in signaling play in different contexts. To this end, **Noboru Mizushima** (Univ. of Tokyo, Japan) presents our current state of understanding of how the interaction between two covalent coupling reactions — activation of Atg5 by attachment of Atg12 and the Atg5-dependent attachment of Atg8 (LC3s and GABARAPs in mammals) to phosphatidylethanolamine — participates in the formation of, cargo recognition by, and maturation of autophagosomes.

In this same regard, we have come to appreciate that what used to be considered simply starting materials, intermediates, or products of metabolic pathways are themselves critical signaling molecules. One way that small-molecule metabolites exert regulatory functions is also via their enzymic attachment to other cellular components, especially the post-translational modification of proteins. Indeed, the combined effects of histone modification and DNA modification, as well as histone variants, can markedly affect gene expression epigenetically. In fact, any mechanism that creates heritable variation, be it an actual mutation or an alteration in epigenetic state, can be exploited to provide a selective advantage to cancer cells over normal tissue. Indeed, as explored in detail by **Joy Bianchia, Xin Zhao, Joseph Mays, and Teresa Davoli** (NYU Langone Health, New York, USA), the driver mutations and supporting genomic alterations that affect the signaling pathways that go awry in cancers are highly tissue-specific. Moreover, there can be direct synergy between these factors; certain genetic mutations drive cancer by affecting metabolism in such a way as to generate novel metabolites that can block normal chromatin modification or even install unusual epigenetic modifications. There are many reasons to suspect that such inter-relationships between metabolism, epigenetics, and disease states, such as cancers, are likely to be much deeper and widespread than currently fully appreciated. For these reasons, **Joyce Liu and Kathryn Wellen** (Univ. of Pennsylvania, Philadelphia, PA, USA) explore just such links by focusing on metabolites responsible for post-translational modifications and epigenetic changes that occur during cancer progression.

Another means by which metabolites can exert regulatory functions is by serving directly as ligands whose interactions with cognate receptors induce allosteric changes that trigger signaling cascades. This latter mechanism is illuminated by **Michael Lückmann, Mette Trauelsen, Thomas Frimurer, and Thue Schwartz** (Univ. of Copenhagen, Denmark), who describe the discovery that certain key metabolites, such as succinate and long-chain fatty acids, can act as extracellular signals of metabolic stress or fuel availability, respectively, via their binding to dedicated G-protein–coupled receptors. At the organelle level, **Katsuhiko Funai, Scott Summers, and Jared Rutter** (Univ. of Utah, Salt Lake City, USA) discuss the often overlooked role of the common lipids that constitute mitochondrial membranes and how they can profoundly influence mitochondrial function.

Of course, the generation and interconversion of metabolites involves many of the other intracellular organelles that are the hallmark of eukaryotic cells. With respect to the critical roles of various intracellular compartments, **Christopher Stefan** (University College London, UK) focuses on the sites of contact between the endoplasmic reticulum and the plasma membrane and the roles that these junctions have in the interplay between the metabolism of the suite of phosphorylated derivatives of phosphatidylinositol (collectively, the phosphoinositides) and signaling events mediated via the regulated sequestration and release of Ca^{2+}, especially in neurons, muscle, and endocrine cells. **Gerald Hammond** (Univ. of Pittsburgh, Pittsburgh, PA, USA) and **John Burke** (Univ. of Victoria, BC, Canada) further describe both known and newly uncovered roles for phosphoinositides in an even wider range of cellular processes and how aberrant phosphoinositide metabolism contributes to multiple human diseases.

Paramount, both historically and functionally, in the elucidation of cellular signal transduction processes has been uncovering the biological roles of the more than 500 protein kinases encoded in the human genome. Here, **Raphael Trenker and Natalia Jura** (Univ. of California, San Francisco, CA, USA) focus on how different ligands for the same member of the human receptor-tyrosine kinase family are able to elicit distinct physiological outputs. **Dario Alessi and Matthew Taylor** (Univ. of Dundee, Scotland, UK) discuss our current understanding of the structure, regulation, and targets of the very large, intracellular, multidomain protein kinase LRRK2, in which dominant missense mutations that hyperactivate its activity are one of the common causes of inherited Parkinson disease.

In this issue, we have also chosen to highlight the impacts of signaling on particular cellular functions. Central to the processes needed to build tissues are the interactions between its constituent cells and the extracellular matrix and other cells. For this reason, **Magdalene Michael and Maddy Parsons** (King's College, London, UK) provide current perspectives on how the heterodimeric transmembrane receptors known as integrins connect sensing of the extracellular matrix to organization of the actin cytoskeleton and other associated regulatory events. How mechanical signals communicated from the cytoskeleton impinge on the structure and function of the nucleus is discussed by **Cátia Janota, Francisco Calero-Cuenca, and Edgar Gomes** (Univ. of Lisbon, Portugal). Similarly, **Coralie Trentesaux, Katharine Striedinger, Jason Pomerantz, and Ophir Klein** (UCSF, San Francisco, USA) discuss our current understanding about the critical role played in stem cell maintenance and renewal by the signaling

cues within the surrounding microenvironment occupied by adult stem cells.

In guiding and responding to cell–cell interactions, signaling processes are nowhere more intricate and extravagant than in the formation and function of the mammalian nervous system and in the proper operation of our immune systems. With respect to nerve tissue, **Yasuhiro Funahashi, Takashi Watanabe, and Kozo Kaibuchi** (Nagoya Univ., Japan) present our current picture of the molecular mechanisms responsible for the establishment of the highly polarized structures — axons and dendrites — in neuronal cells, especially how advances in phospho-proteomics and gene transfer technology have enabled comprehensive analysis of the signaling molecules involved. **Stephanie Gupton and Laura McCormick** (Univ. of North Carolina, Chapel Hill, NC, USA) discuss what has been uncovered recently about how the growth cone of a neuron directs the navigation necessary for an axon to establish appropriate connectivity with its correct synaptic partners to generate a functional nervous system.

With regard to operation of our immune system, the factors involved range from the roles played in innate immune response to pathogens by a ubiquitous class of small molecules, the cyclic dinucleotides, as discussed by **Shivam Zaver and Joshua Woodward** (Univ. of Washington, Seattle, USA), to the higher order supramolecular complexes that carry out key signaling and effector functions in innate immunity and inflammation, some of which assemble through intrinsically disordered regions of biomolecules, resulting in condensates that undergo liquid-like phase separation, as presented by **Ming Shi**, **Pengfei Zhang,** and **Hao Wu** (Harvard Med. Sch., Boston USA). Continuing with this focus, innate immune cells and their daughters retain a 'memory' of their prior challenges, increasing their capacity for resolving inflammation. The epigenetic and metabolic rewirings of cellular state responsible for this behavior, in particular the role of a novel class of long noncoding RNAs, are described by **Jorge Domínguez-Andrés, Stephanie Fanucchi, Leo Joosten, Musa Mhlanga, and Mihai Netea** (Radboud Univ., Nijmegen, Netherlands). Finally, all of our other cells begin their life after the successful merger of a sperm with an egg and the subsequent divisions of the resulting zygote. That initial encounter depends critically on sperm motility and the signaling cues and processes needed for the sperm flagellum to function optimally, as recounted by **Lenka Vyklicka and Polina Lishko** (Univ. of California, Berkeley, USA). Conversely, different cells in different tissues under different circumstances have many different ways to end their existence, and **Robin Schwarzer, Lucie Laurien, and Manolis Pasparakis** (Univ. of Cologne, Germany) discuss several of these death mechanisms, as well as new insights into and unexpected links between these pathways.

As these articles reinforce, cell signalling is an integral feature in all aspects of cell biology.

Conflict of interest statement

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ceb.2020.02.013.